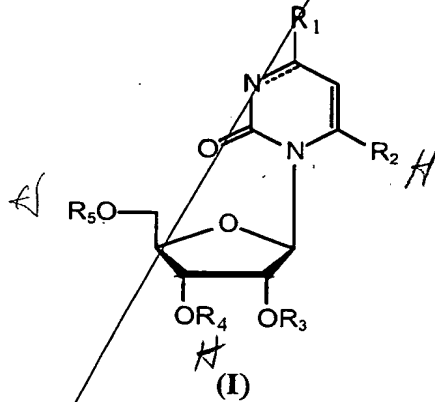
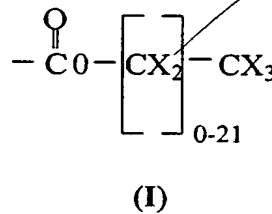


WHAT IS CLAIMED IS:

- ① A method for the treatment of a mitochondrial disorder comprising administering to a subject having or at risk of having such disorder an effective amount of a compound of Formula I:



wherein:
 R₁ is OH, NHC(=O)CH₃, or NH₂,
 R₂ is H, CO₂H, or



wherein:

X is C₁-C₂₂ alkyl, C₁-C₂₂ alkenyl or C₁-C₂₂ alkynyl, with substituents selected from the group consisting of H, C₁₋₃ alkyl, OH, NH₂, and halogen, or wherein X is H,

R₃, R₄, and R₅ are, independently, optionally substituted C₁-C₂₂ alkyl carbonyl, with substituents selected from the group consisting of C₁₋₃ alkyl, OH, NH₂, halogen, and H, wherein at least one of R₃, R₄, and R₅ is not H,

thereby treating the disorder.

- ② A method for the treatment of a mitochondrial disorder comprising administering to a subject having or at risk of having such disorder, an effective amount of 2', 3', 5'-tri-O-acetyl-1-β-D-uridine. This compound is included in cl 1.

triaethyluridine

PN 401

Scab
Cl 1

No salts

not defined

not uridine
not uridine
not uridine

09889251 110101



3. A method according to claim 1 or claim 2, wherein the optionally substituted alkyl carbonyl is unbranched and has in the range of about 5 to 22 carbons.

4. A method according to claim 1, wherein the alkyl carbonyl is a carbonyl derivative of an amino acid selected from the group consisting of glycine, L-forms of alanine, valine, leucine, isoleucine, tyrosine, proline, hydroxyproline, serine, threonine, cystine, cysteine, aspartic acid, glutamic acid, arginine, lysine, histidine, carnitine, and ornithine.

5. A method according to claim 1, wherein the alkyl carbonyl is a carbonyl derivative of a dicarboxylic acid having in the range of about 3 to 22 carbons.

6. A method according to claim 1, wherein the mitochondrial disorder comprises a mutation in mitochondrial or nuclear DNA.

7. A method according to claim 1 or claim 2, wherein the mitochondrial disorder is selected from the group consisting of:

- Huntington's disease,
- Amyotrophic lateral sclerosis,
- MELAS (Mitochondrial encephalomyopathy with lactic acidemia and stroke-like episodes),
- ✓ MERRF (Myoclonus, epilepsy, and myopathy with ragged red fibers),
- NARP/MILS (Neurogenic muscular weakness, ataxia, retinitis pigmentosa/Maternally inherited Leigh syndrome),
- LHON (Lebers hereditary optic neuropathy) "Mitochondrial blindness",
- KSS (Kearns-Sayre Syndrome),
- PMPS (Pearson Marrow-Pancreas Syndrome),
- CPEO (Chronic progressive external ophthalmoplegia),
- ✓ Leigh syndrome,
- ✓ Alpers syndrome,
- Multiple mtDNA deletion syndrome,
- MtDNA depletion syndrome,
- Complex I deficiency,
- Complex II (SDH) deficiency,

6213

0989251 110101

Subj
C. 2
Jul 11

R3 R4 R5

carbonyl

Complex III deficiency, Cytochrome c oxidase (COX, Complex IV) deficiency,
 Complex V deficiency,
 Adenine Nucleotide Translocator (ANT) deficiency,
 Pyruvate dehydrogenase (PDH) deficiency,
 Ethylmalonic aciduria with lactic acidemia,
 3-Methyl glutaconic aciduria with lactic acidemia,
 Refractory epilepsy with declines during infection,
 Asperger syndrome with declines during infection,
 Autism with declines during infection,
 Attention deficit/hyperactivity disorder (ADHD),
 Cerebral palsy with declines during infection,
 Dyslexia with declines during infection, maternally inherited thrombocytopenia
 and leukemia syndrome,
 MNGIE (Mitochondrial myopathy, peripheral and autonomic neuropathy,
 gastrointestinal dysfunction, and epilepsy),
 MARIAHS syndrome (Mitochondrial ataxia, recurrent infections, aphasia,
 hypouricemia/hypomyelination, seizures, and dicarboxylic aciduria),
 ND6 dystonia,
 Cyclic vomiting syndrome with declines during infection,
 3-Hydroxy isobutyric aciduria with lactic acidemia,
 Diabetes mellitus with lactic acidemia, — *hormonal*
 Uridine responsive neurologic syndrome (URNS),
 Familial Bilateral Striatal Necrosis (FBSN),
 Aminoglycoside-associated deafness,
 Dilated cardiomyopathy,
 Splenic Lymphoma,
 Wolfram syndrome,
 Multiple mitochondrial DNA deletion syndromes, and
 Renal Tubular Acidosis/Diabetes/Ataxia syndrome.

8. A method according to claim 1 or claim 2, wherein the mitochondrial disorder is a deficiency of cardiolipin.
9. A method according to claim 1 or claim 2, wherein the mitochondrial disorder comprises a deficiency in a pyrimidine synthetic pathway.

TOP SECRET

Handwritten initials/signature

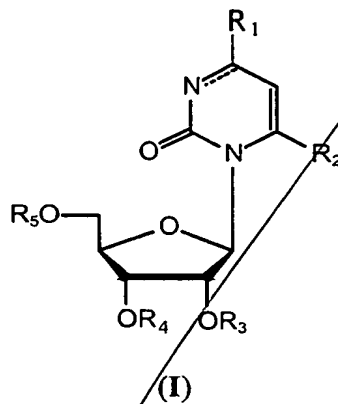
Sub
Off
amt

- 21. A method according to claim 19, wherein the vitamin is selected from the group consisting of thiamine (B1), riboflavin (B2), niacin (B3), pyridoxine (B6), folate, cyanocobalamin (B12), biotin, and pantothenic acid.
- 22. A method according to claim 1, wherein the compound of Formula (I) is administered in a daily dosage in the range of about 0.5 g/m² to 20 g/m².
- 23. A method according to claim 1, wherein the compound of Formula (I) is administered in a daily dosage in the range of about 2 g/m² to 10 g/m².
- 24. A method according to claim 1, wherein the compound of Formula (I) is administered in a daily dosage of about 6.0 g/m².

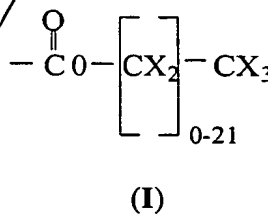
TOP SECRET

Sub
Off

- 25. A method for reducing or eliminating one or more symptoms associated with a mitochondrial disorder comprising administering to a subject in need thereof an effective amount of a compound of Formula I:



wherein:
 R₁ is OH, NHCOCH₃, or NH₂,
 R₂ is H, CO₂H, or



wherein:

CS
ent

X is C₁-C₂₂ alkyl, C₁-C₂₂ alkenyl or C₁-C₂₂ alkynyl, with substituents selected from the group consisting of H, C₁₋₃ alkyl, OH, NH₂, and halogen, or wherein X is H,

R₃, R₄, and R₅ are, independently, optionally substituted C₁-C₂₂ alkyl carbonyl, with substituents selected from the group consisting of C₁₋₃ alkyl, OH, NH₂, halogen, and H, wherein at least one of R₃, R₄, and R₅ is not H,

thereby treating the disorder.

US 5,950,000
D.F.

26. A method for reducing or eliminating one or more symptoms associated with a mitochondrial disorder comprising administering to a subject having or at risk of having such disorder, an effective amount of triacetyluridine.

27. A method according to claim 25 and claim 26, wherein the symptoms are renal tubular acidosis (RTA), impaired eyesight, dementia, seizures, cardiomyopathy, skeletal myopathy, peripheral myopathy or autonomic myopathy.

Add B17

Add C11